DETAILED ACTION

Receipt of amendment and response dated 1-22-08 is acknowledged.

Claims 1-34 and 38-71 have been canceled. Claims 35-37 are pending in the instant application.

Response to Arguments

1. Applicant's arguments filed 1-22-08 have been fully considered but they are not persuasive. Accordingly, the following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0127277 to Qiu et al in view of Remingtons' Pharmaceutical Sciences (cited in the previous action) OR

Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0127277 to over Qiu and Remingtons' in view of US 5,0449,586 to Ortega et al (Ortega) OR

Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,049,586 to Ortega et al in view of US 2002/0127277 and Remingtons'.

Qiu teaches compressed tablets comprising valproic acid or its derivatives such as valproate compounds ([0019-0040), all of which within the scope of the claimed active agents. Qiu teaches granulating the active agent by mixing with a binder and

finally preparing compressed tablet or capsule formulation (0041-0044). The composition also contains excipients such as diluents (which include the same compounds as instant fillers), lubricants, disintegrants such as the claimed croscarmellose, glidants, binders etc (0046-0051). Qiu teaches that the quantity of each excipient that is blended with the active agent varies and is in the range of 20-50% with the active agent varying between 50-80% (0054- 0055). Qiu states that the granulation technique is suitable for both immediate and delayed release tablets (0068). Example 1, described by Qiu includes sodium starch glycolate as a disintegrant, povidone (binder), microcrystalline cellulose etc. Further Qiu teaches that the tablet of example 1 results in rapid dissolution (>90% on 20 minutes) (0083) and thus is an immediate release dosage form because Qiu states that the drug being soluble, permeable and stable has an equivalent in vivo absorption (Fig. 1). Qiu recognizes valproic acid for the treatment of mania, pain, epilepsy etc., all of which have been claimed in the instant application (0010).

Qiu fails to teach the claimed hydroxypropyl cellulose among the binders.

Remingtons' Pharmaceutical Sciences (Remingtons') teach oral dosage forms, particularly, compressed tablets comprising the tabletting excipients such as diluents, binders, disintegrants, glidants etc (pages 134-1637). Among the binder materials employed in compressible tablets, Remingtons' suggests cellulose materials such as hydroxy ethylcellulose (HEC) and hydroxypropyl cellulose (HPC), in addition to PVP, HPMC, starch, gelatin etc (page 1636). Thus, Remingtons' teaches equivalence of the binder materials of Qiu with that of HPC and HEC.

Thus, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use any of the binding materials such as starch, PVP, HPMC (of Qiu) or HPC or (Remingtons') in the compressible tablets of Qiu because Remingtons' suggests that HC or HEC are also successful as binding materials, for imparting cohesive qualities and also improve the flow properties. Further, with respect to the composition claims containing specific amounts of fillers, active agent and the disintegrants, Qiu suggests a range of the amounts for the active and the excipients and accordingly a skilled artisan would have been able to optimize the amounts of the individual excipients in the composition of Qiu depending on the hardness of the tablet, friction, flow characteristics and the amount of disintegration required.

Ortega teaches valproic acid containing compressed tablets comprising excipients such as binders, disintegrants, lubricants, fillers etc, which include compounds such as those claimed in the instant claims (see abstract, example composition in col. 1, L 45-68; col. 2, 14-68 and example 1. The composition of Ortega results in immediate dissolutions, as seen from the plasma levels found in the table of col. 4-5, thus suggesting an immediate release of the drug. Thus, immediate release compositions of valproic acid are not novel in the art and therefore a skilled artisan would have been able to prepare either an immediate or a delayed release composition from the composition of Qiu, by incorporating HPC or other appropriate cellulose (of Remingtons and Qiu) depending on the type of release desired with the valproic acid or its derivatives, for the treatment of epilepsy.

Alternatively, Ortega teaches valproic acid but not valproic acid salts or the derivatives. Ortega also lacks the claimed HPC. Qiu, discussed above teaches valproic acid or valproate compounds such as those claimed, as suitable for preparing the immediate release compressed tablets. Remingtons' discuss the role of HPC as a successful binder and suggests that it is equally efficient as other binders in improving the flow characteristics. Therefore, a skilled artisan would have been able to employ valproic acid or its derivatives such as valproate, as an active agent and any of the binders such as HPC or PVP, in the composition of Ortega and still obtain the same rapid release of the active agent because Qiu and Remington teach the above for immediate release compositions.

2. **RESPONSE TO ARGUMENTS**: Applicants' arguments are as follows:

3. Applicants respectfully traverse rejections (A)-(C), above. The rejections are moot in view of canceled claims 1-34 and 38-55. Further, no combination of the references discloses or suggests the formulations recited in claims 35-37. Claim 35 is directed to: (a) uniform admixture of 500 mg/tablet N-(2-Propylpentanoyl) glycinamide; 50 mg/tablet hydroxypropyl cellulose; and 100 mg/tablet a microcrystalline cellulose, and (b) 55 mg/tablet croscarmellose sodium; 145 mg/tablet lactose; and 6 mg/tablet magnesium stearate. Claim 36 is directed to: (a) a uniform admixture of 500 mg/tablet N-(2-Propylpentanoyl) glycinamide; 50 mg/tablet hydroxypropyl cellulose; and 100 mg/tablet a microcrystalline cellulose, and (b) 50 mg/tablet croscarmellose sodium; 145 mg/tablet lactose; and 6 mg/tablet magnesium stearate. Claim 37 is directed to: (a) a uniform admixture of 250 mg/tablet N-(2-Propylpentanoyl) glycinamide; 25 rag/tablet

hydroxypropyl cellulose; and 50 mg/tablet microcrystalline cellulose; (b) 450 rag/tablet microcrystalline cellulose; 50 mg/tablet croscarmellose sodium; and 6 mg/tablet magnesium stearate. No combination of the references discloses or suggests an immediate release tablet comprising the specific components in the specific amounts recited in claims 35-37. There would be far less than a reasonable expectation that an ordinarily skilled artisan would select N-(2- Propylpentanoyl) glycinamide as the active agent from among valproic acid and derivatives thereof disclosed in the '277 application, and combine it with microcrystalline cellulose, croscarmellose sodium lactose, and magnesium stearate (also disclosed in '277), and then look to Remingtons' and select hydroxypropyl cellulose from among all the disclosed cellulose materials. Even less likely is the expectation that an ordinarily skilled artisan would combine these components in the recited uniform admixture and in the recited amounts. The '586 patent does not disclose N-(2- Propylpentanoyl) glycinamide nor does it suggest the specific combination of excipients recited in claims 35-37. Thus, no combination of the references discloses or suggests the claimed formulations. Accordingly, for the reasons stated above, the obviousness rejections should be withdrawn.

Applicants' arguments are not persuasive because the '277 reference clearly teaches immediate release formulations of valproic derivatives that are prepared by the methods first granulating the compound in the presence of excipients, milling, drying and blending with additional excipients before compressing into tablets (paragraphs 0044-0051, 0063 and 0068). Thus, '277 recognize all of the

pharmaceutical excipients required to produce an immediate release tablet containing the active agent valproic acid and its derivatives. With respect to the specific amounts of the excipients claimed, '277 reference teaches a range of percentages for the excipients that can be suitably employed in preparing a tablet dosage form. The examples of '277 also shows an immediate release of the drug i.e., >90% in 20 minutes (fig. 1). '277 recognizes the same ingredients i.e., lubricants, disintegrants, binders etc., that are also employed in preparing the instant tablet compositions. Similarly, the teachings of Ortega suggest immediate release compressed tablets of, except the claimed HPC as a binder. However, Remingtons' establishes the equivalence of various binders including hydroxypropyl cellulose that can be employed in compressed dosage forms. Applicants have not established any unexpected or superior result in employing the claimed HPC as a binder as opposed to the other binders and hence choosing an appropriate binder material in preparing the claimed tablet formulation so as to obtain the desired flow property of the formulation would have been within the scope of a skilled artisan. With respect to the argument regarding the exact amounts of individual components in the instant claims, the prior art if record recognizes all of the claimed elements and it is well settled that general differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to

discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, a skilled artisan would have readily been able to optimize the amounts of individual excipients in preparing an immediate release compressed tablet containing the claimed active agent with an expectation to achieve the desired release rate of the drug.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner,
Art Unit 1611
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